FORM PTO-1390
(REV 10-94)

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

DOCKET #: 4271-29PUS

09/ 674800

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP99/03029	**04 May 1999**	**06 May 1998**

TITLE OF INVENTION

Transdermal Therapeutic System for the Administration of Candesartan

APPLICANT(S) FOR DO/EO/US

Thomas STRÜNGMANN

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [x] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371
3. [x] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [x] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [x] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [] has been transmitted by the International Bureau.
   c. [] is not required, as the application was filed in the United States Receiving Office (RO/US)
6. [x] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [x] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [] have been transmitted by the International Bureau.
   c. [] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [x] have not been made and will not be made.
8. [] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [x] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. Below concern other document(s) or information included:

11. [] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [x] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [x] A **FIRST** preliminary amendment.
    [] A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. [] A substitute specification.
15. [] A change of power of attorney and/or address letter.
16. [x] Other items or information *(specify):* PCT Publication Sheet, Int'l Preliminary Examination Report, Int'l Search Report

U S APPLICATION NO. (If known, see 37 C.F.R. 1.5) 09/ 674800	INTERNATIONAL APPLICATION NO. PCT/EP99/03029	ATTORNEY'S DOCKET NUMBER 4271-29PUS

17.[x]The following fees are submitted:

Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO ..... **$860.00** International preliminary examination fee paid to USPTO (37 CFR 1.482)..... **$690.00** No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... **$710.00** Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... **$1000.00** International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$**	860
Surcharge of **$130.00** for furnishing the oath or declaration later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$**	

Claims	Number Filed	Number Extra	Rate		
Total Claims	16 - 20 =		x **$18.00**	**$**	
Independent Claims	1 - 3 =		x **$80.00**	$	
Multiple dependent claim(s) (if applicable)			+ **$270.00**	**$**	
TOTAL OF ABOVE CALCULATIONS =				**$**	860
Reduction of ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				**$**	
SUBTOTAL =				**$**	860
Processing fee of **$130.00** for furnishing the English translation later than [] 20 [] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				**$**	
TOTAL NATIONAL FEE =				**$**	860
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by the appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				**$**	40
TOTAL FEES ENCLOSED					$900
Amount to be refunded:					**$**
charged:					**$**

a. [x]Two check(s) in the amount(s) of $ 860 and $ 40 to cover the above fees is/are enclosed.
b. [] Please charge my Deposit Account No. 03-2412 in the amount of $____ to cover the above fees. A duplicate copy of this sheet is enclosed.
c. [x]The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 03-2412. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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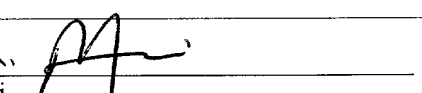

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By Express Mail # EL489905598US · November 6, 2000

Attorney Docket # 4271-29PUS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re National Phase PCT Application of

Thomas STRÜNGMANN

International Appln. No.: PCT/EP99/03029

International Filing Date: May 04, 1999

For: Transdermal Therapeutic System for the Administration of Candesartan

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231
BOX PCT

S I R:

Prior to examination of the above-identified application please amend the application as follows:

In the Specification:

Page 1, line 1 delete the title and input therefore **--Transdermal Therapeutic System for the Administration of Candesartain--**;

Page 1, following line 3, insert as a centered heading

--Background Of The Invention--

Page 3, following line 8, insert as a centered heading

--**The Invention**--;

Page 4, line 9, delete "to have" in its second occurrence;

Page 11, following line 20, insert as a separate paragraph --The terms and expressions which have been employed are used as terms of description and not of limitation, and there is no intention in the use of such terms and expressions of excluding any equivalent of the features shown and described or portions thereof, it being recognized that various modifications are possible within the scope of the invention.--.

In the Claims:

Without prejudice, cancel claims 1 to 15 and add claims 16 to 31.

--16. A transdermal therapeutic system with a content of a first active ingredient selected from candesartan or one of its pharmaceutically suitable esters or salts.

17. The transdermal therapeutic system of claim 16 wherein candesartan is the active ingredient.

18. The transdermal therapeutic system of claim 16 wherein candesartan cilexetil is the active ingredient.

19. The transdermal therapeutic system of claim 16 wherein an ammonium and/or alkali metal salt of candesartan is the active ingredient.

20. The transdermal therapeutic system of claim 16 further comprising at least a second active ingredient.

21. The transdermal therapeutic system of claim 20 wherein the second active ingredient enhances the effect of candesartan.

22. The transdermal therapeutic system of claim 20 wherein the second active ingredient is a diuretic and/or a Ca channel blocker.

23. The transdermal therapeutic system of claim 16 in the form of a plaster with an impermeable covering layer and a detachable protective layer, in particular in the form of a matrix system or of a membrane system.

24. The transdermal therapeutic system of claim 23 wherein the covering layer comprises a polyester, polypropylene, polyurethane or polyethylene, and is optionally metalized or pigmented.

25. The transdermal therapeutic system of claim 23 wherein the detachable protective layer comprises a polyester, polypropylene, polysiloxane, polyacrylate, ethylene/vinyl acetate, polyurethane, polyisobutene or paper with a silicone and/or a polyethylene coating.

26. The transdermal therapeutic system of claim 23 wherein the system is a matrix system comprising:

an impermeable covering layer;

at least one active ingredient-containing contact adhesive matrix layer or at least one ingredient-containing matrix layer coated with a contact adhesive;

a detachable protective layer; and

an active ingredient selected from candesartan or one of its pharmaceutically acceptable esters or salts.

27. The transdermal therapeutic system of claim 26 wherein the matrix layer comprises a polyacrylate, silicone, polyisobutylene, rubber, rubber-like synthetic homo-, co- or block polymers, butyl rubber, styrene/isoprene copolymer, polyurethanes, copolymers of ethylene, polysiloxanes or styrene/butadiene copolymer.

28. The transdermal therapeutic system of claim 23 wherein the membrane system comprises:

an impermeable covering layer;

an active ingredient-containing reservoir or an active ingredient-containing reservoir layer;

a microporous or semipermeable membrane;

an optional contact adhesive layer; and

an active ingredient selected from candesartan or one of its pharmaceutically acceptable esters or salts.

29. The transdermal therapeutic system of claim 28 wherein the membrane comprises an inert polymer, in particular polypropylene, polyvinyl acetate, polyamide, ethylene/vinyl acetate copolymer or silicone.

30. The transdermal therapeutic system of the claim 16 further comprising a permeation promoter.

31. The transdermal therapeutic system of claim 30 wherein the permeation promoter is elected from the group consisting of monohydric and/or polyhydric aliphatic, cycloaliphatic and/or aromatic-aliphatic alcohols each with up to 8 C atoms, and/or polyethylene glycol; alcohol/water mixtures; saturated and/or unsaturated fatty alcohols each with 8-18 C atoms; terpenes; mixtures of terpenes and ethanol and/or propylene glycol; tea tree oil; saturated and/or unsaturated cyclic ketones; alkyl methyl sulfoxides; saturated and/or unsaturated fatty acids each with 8-18 C atoms; the esters and salts thereof; natural vitamin E; synthetic vitamin E and/or vitamin E derivatives; sorbitan fatty acid esters and ethoxylated sorbitan fatty acid esters; Azone (laurocapram); Azone mixed with alcohols; urea; 1-alkylpyrrolidone; block copolymers of polyethylene glycol and dimethylsiloxane with cationic groups at one end; folate-polyethylene glycol liposome, proliposome; polyoxyethylene 10 stearyl ether; mixture of polyoxyethylene 10 stearyl ether and glyceryl dilaurate; dodecyl 2-(N,N-dimethylamino)propanoltetradecanoate and/or dodecyl 2-(N,N-dimethylamino)propionateN-acetylprolinate esters with more than 8 C atoms; nonionic surfactants, esters of polyoxyethylene; ethosome (phospholipid vesicle); dimethyl(arylimino)sulfurane; mixture of oleic acid analogs and propylene glycol; mixture of padimate O, octyl salicylate, octyl methoxycinnamate and laurocapram and/or mixtures thereof.

REMARKS

The specification and claims of the above-identified application have been amended to a form more consistent with U.S. practice. No new matter has been added.

Early examination and favorable consideration of the above-identified application is earnestly solicited.

Any additional fees or charges required at this time in connection with the application may be charged to our Patent and Trademark Office Deposit Account No. 03-2412.

Respectfully submitted,
COHEN, PONTANI, LIEBERMAN & PAVANE

By: _____

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6 November 2000

Transdermal therapeutic system for administration of candesartan

The invention relates to an active ingredient-containing transdermal system for administration of candesartan and/or its pharmaceutically suitable esters and/or salts.

Candesartan (2-ethoxy-1-[[2'-(1H-tetrazol-5-yl)biphenyl-4-yl]methyl]benzimidazole-7-carboxylic acid) is a highly specific, non-peptide angiotensin II receptor antagonist. It has a high specificity and a strong affinity for the AT_1 receptor and a long duration of binding, and thus a long-lasting activity. Candesartan is mainly used to treat essential hypertension (non-organ-related high blood pressure), heart diseases, strokes, nephritis (EP-0459136 B1) and left ventricular hypertrophy.

On oral administration, the ester (candesartan cilexetil) of candesartan and 1-(cyclohexyloxycarbonyl-oxy)ethanol is used as prodrug (EP-0459136 B1) in order to ensure the stability necessary for passing through the stomach and thus increase the bioavailability (Kubo, K.; Kohara, Y. and co-workers; J. of Medicinal Chemistry; 36 (16) 2343-2349/1993). This ester is converted completely by ester hydrolysis in the gastrointestinal tract into its active form candesartan which is 30% more active than the ester. Candesartan is then extensively distributed in the tissue and

in blood vessels. The elimination of candesartan from the blood vessel walls takes place considerably more slowly than from the plasma, resulting in the long-lasting effect. Candesartan is partly metabolized further to inactive metabolites in the liver. Candesartan and its metabolites are then, after hepatobiliary passage, excreted with feces and urine. The ester side chain of candesartan cilexetil which is eliminated in the intestine is absorbed and distributed in the tissue mainly as cyclohexanol. In the liver there is then degradation to cyclohexanediol, cyclohexanetriol and other degradation products. The bioavailability of candesartan in this case is only 14%. The maximum therapeutic effect on oral intake is reached after 4 weeks because a gradual reduction in blood pressure takes place through the slow occupation of the receptors.

To date candesartan cilexetil has been administered exclusively orally or intravenously. Since candesartan is degraded by gastric acid during passage through the stomach, either the active ingredient must be esterified or an elaborate dosage form, such as, for example, an enteric coating, must be produced. This results in additional costs both for the machines and workforce and for the additionally required material. The bioavailability of active ingredients on oral administration is frequently unsatisfactory. In this case, it is only 14%. The hepatic metabolism of the active ingredient on first passage through the liver may lead to

unwanted concentration conditions and toxic byproducts, and to a reduction in the effect.

The object of the present invention is now to provide a transdermal system for systemic administration of candesartan and/or one of its pharmaceutically suitable esters or salts, the intention being to avoid the disadvantages of oral or intravenous administration forms used to date.

It has now been found, surprisingly, that candesartan and/or its pharmaceutically suitable esters and salts can be administered by means of a transdermal therapeutic system in such a way that a therapeutically effective blood level is reached. The possibility of using the active ingredient candesartan and/or its pharmaceutically suitable esters and salts, which display a direct systemic effect, makes it possible to increase considerably the bioavailability and greatly reduce the dose level. The stress on the body and the adverse effect on the liver due to the metabolism can thus be considerably reduced. The use of a transdermal therapeutic system makes controlled delivery of active ingredient possible, so that large blood plasma variations can be avoided and a constant blood plasma level can be guaranteed even for several days. The optimal effect of the active ingredient is thus achieved conveniently and reliably. The maximum therapeutic effect is reached after only 3 weeks.

It is likewise to be regarded as advantageous that the use of plasters is simple and convenient by comparison with oral or intravenous administration. Since the system is applied externally, it can carry out its intended function in this way for a very long time without being changed. This is completely impossible with oral systems because they leave the body through the digestive tract after one day at the longest. In addition, it is simpler and more pleasant for the patient to have to have to think of taking the medicine only 1-2 times a week instead of having to take a tablet once a day.

The object on which the invention is based is now achieved by a transdermal therapeutic system with a content of candesartan and/or one of its pharmaceutically suitable esters or salts, in particular by candesartan and/or candesartan cilexetil.

Possible and suitable salts of candesartan are, in particular, alkali metal salts such as, for example, the potassium, sodium and lithium salts, and the ammonium salt.

Candesartan and/or one of its pharmaceutically acceptable esters or salts as active ingredient can moreover be administered in combination with other known active ingredients, especially diuretics and Ca channel blockers, for example hydrochlorothiazide (HCTZ) or amlodipine. These active ingredients exert an additive antihypertensive effect.

The transdermal therapeutic system according to the invention may be in the form of a plaster. This plaster may be a matrix or membrane system which has an impermeable covering layer and a detachable protective layer. A suitable constituent of the impermeable covering layer is polyester, polypropylene, polyurethane or polyethylene, each of which may be metalized or pigmented if required. Suitable for the detachable protective layer are polyester, polypropylene, polysiloxane, polyacrylate, ethylene/vinyl acetate, polyurethane, polyisobutene or paper with silicone and/or polyethylene coating.

The matrix plaster may consist of an impermeable covering layer, of one or more than one self-adhesive matrix layer which contains the active ingredient and/or one of its pharmaceutically suitable esters or salts and, where appropriate, other active ingredients and/or permeation promoters and/or amino acids, or of a matrix layer which is coated with a contact adhesive, and of a detachable protective layer. The active ingredient present in the matrix may be candesartan and/or its pharmaceutically suitable ester or salts and, in the case of combination, additionally other active ingredients such as Ca channel blockers or diuretics, for example amlodipine or HCTZ.

It is possible to use for the matrix the matrix formers usual in medicine, such as polyacrylate, silicone, polyisobutylene, rubber, rubber-like synthetic homo-, co- or

block polymers, butyl rubber, styrene/isoprene copolymer, polyurethanes, copolymers of ethylene, polysiloxanes or styrene/butadiene copolymer.

A further embodiment of the invention is in the form of a membrane system. This may consist of an impermeable covering layer, of an active ingredient-containing reservoir or of a reservoir layer, of a semipermeable membrane, of an optional contact adhesive layer and of a detachable protective layer. The reservoir may contain candesartan and/or one of its pharmaceutically suitable esters or salts, where appropriate other active ingredients and/or permeation promoters, stabilizers, emulsifiers, thickeners and/or conventional membrane system or reservoir plaster aids. The reservoir or the reservoir layer is located between the covering layer and the membrane. Gel formers which can be used if required are methylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, carboxyvinyl polymer, sodium glyoxylate, carboxymethylcellulose or a mixture of these.

The membrane, which normally consists of inert polymers, in particular based on polypropylene, polyvinyl acetate, polyamide, ethylene/vinyl acetate copolymers or silicone, may, depending on the pore size, have a controlling effect on release of active ingredient.

It is possible to choose for the contact adhesive layer of the matrix or membrane system according to the invention which is described above a pressure-sensitive

adhesive, for example a polyurethane-based, polyisobutylene-based, polyvinyl ether-based, silicone-based or acrylate-based one.

The silicone-based adhesive may be a silicone adhesive which is based on two main constituents, a polymer or adhesive, in particular polysiloxane, and a tack-increasing resin. The polysiloxane adhesive is usually prepared with a crosslinker for the adhesive, typically with a high molecular weight polydiorganosiloxane, and with the resin, in order to afford a three-dimensional silicate structure via an appropriate organic solvent. Addition of the resin to the polymer is the most important factor for altering the physical properties of the polysiloxane adhesives; cf., for example, Sobieski, et al., "Silicone Pressure Sensitive Adhesives", Handbook of Pressure Sensitive Adhesive Technology, 2nd ed., pp. 508-517 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).

Another example of a pressure-sensitive silicone-based adhesive is trimethylated silicon dioxide which has been treated with polydimethylsiloxane with terminal trimethylsiloxy groups.

The acrylate-based adhesives can be any homopolymer, copolymer or terpolymer consisting of various acrylic acid derivatives.

Thus, the acrylate polymers can be polymers of one or more monomers of acrylic acids and other copolymerizable

monomers. The acrylate polymers may additionally comprise copolymers of alkyl acrylates and/or alkyl methacrylates and/or copolymerizable secondary monomers or monomers with functional groups. It is possible by altering the amount of each type of monomer added to alter the cohesive properties of the acrylate polymers resulting therefrom. In general, the acrylate polymer consists of at least 50% by weight of an acrylate, methacrylate, alkyl acrylate or alkyl methacrylate monomer, 0 to 20% of a functional monomer copolymerizable with acrylate, and 0 to 40% of another monomer.

Acrylate monomers which can be used with acrylic acid, methacrylic acid, butyl acrylate, butyl methacrylate, hexyl acrylate, hexyl methacrylate, isooctyl acrylate, isooctyl methacrylate, 2-ethylhexyl acrylate, 2-ethylhexyl methacrylate, decyl acrylate, decyl methacrylate, dodecyl acrylate, dodecyl methacrylate, tridecyl acrylate and tridecyl methacrylate are listed below.

Thus, functional monomers copolymerizable with the above-mentioned acrylates, methacrylates, alkyl acrylates or alkyl methacrylates can be employed, for example acrylic acid, methacrylic acid, maleic acid, maleic anhydride, hydroxyethyl acrylate, hydroxypropyl acrylate, acrylamide, dimethylacrylamide, acrylonitrile, dimethylaminoethyl acrylate, dimethylaminoethyl methacrylate, tert-butylaminoethyl acrylate, tert-butylaminomethyl methacrylate, methoxyethyl acrylate and methoxyethyl methacrylate.

Further details and examples of pressure-sensitive acrylates suitable for the invention are described in Satas Handbook of Pressure Sensitive Adhesive Technology "Acrylic Adhesives", 2nd ed., pp. 396-456 (D. Satas, ed.), Van Nostrand Reinhold, New York (1989).

Permeation promoters which can be used are monohydric and/or polyhydric aliphatic, cycloaliphatic and/or aromatic-aliphatic alcohols each with up to 8 C atoms, for example ethanol, 1,2-propanediol, dexpanthenol and/or polyethylene glycol; alcohol/water mixtures; saturated and/or unsaturated fatty alcohols each with 8-18 C atoms; terpenes; for example cineol, carveol, menthone, terpineol, verbenone, menthol, limonene, thymol, cymene, terpinen-4-ol, neomenthol, geraniol, fenchone; mixtures of terpenes and ethanol and/or propylene glycol; tea tree oil; saturated and/or unsaturated cyclic ketones; alkyl methyl sulfoxides; saturated and/or unsaturated fatty acids each with 8-18 C atoms; the esters and salts thereof; natural vitamin E; synthetic vitamin E and/or vitamin E derivatives; sorbitan fatty acid esters and ethoxylated sorbitan fatty acid esters; Azone (laurocapram); Azone mixed with alcohols; urea; 1-alkylpyrrolidone; block copolymers of polyethylene glycol and dimethylsiloxane with cationic groups at one end; folate-polyethylene glycol liposome, proliposome; polyoxyethylene 10 stearyl ether; mixture of polyoxyethylene 10 stearyl ether and glyceryl dilaurate; dodecyl 2-(N,N-dimethylamino)propanoltetra-

decanoate and/or dodecyl 2-(N,N-dimethylamino)propionate; N-acetylprolinate esters with more than 8 C atoms; nonionic surfactants, for example lauryl ethers, esters of polyoxyethylene; ethosome (phospholipid vesicle); dimethyl(arylimino)sulfurane; mixture of oleic acid analogs and propylene glycol; mixture of padimate O, octyl salicylate, octyl methoxycinnamate and laurocapram and/or mixtures of all these components.

The invention is explained in detail by the following examples without, however, restricting the scope of the invention thereby.

Example 1 (matrix plaster)

11.1 g of candesartan cilexetil are dissolved in 75 g of extra pure acetone, and 8 g of Copherol F1300 are added. The clear solution is added to 169 g of an approx. 36% strength acrylate copolymer (Duro-Tak 387-2353, Nat. Starch & Chemical B.V.) and stirred. The homogeneous solution is spread on a siliconized polyester sheet (for example 75 µm) or on siliconized paper and dried at 35°C to 85°C to result in a matrix dry weight of 80 ± 10% g/m^2. The detachable protective layer (for example polyester 15 µm) is then laminated onto the matrix side.

TTS with an area of 20 cm^2 are punched out.

A plaster of this size contains 16 mg of candesartan and 16 mg of α-tocopherol.

Example 2 (reservoir plaster) (see drawing)

Firstly 138.4 g of candesartan cilexetil are dissolved in 861.6 g of a mixture of ethanol abs. 65% (V/W), Copherol F1300 10% (V/W) and hydroxypropylcellulose 1% (V/W) with stirring. This mixture is the active drug solution for the reservoir. The reservoir is charged with 400 ± 5% mg of the active drug solution.

The transdermal therapeutic system (see drawing) consists firstly of the optional adhesive layer which forms the adhesive ring. Onto this layer is applied a heat-sealable, impermeable covering layer. On the side facing the skin, the reservoir is affixed to the covering layer and sealed with a microporous EVA membrane (Cotran 9702, 3M). A siliconized PET sheet serves as detachable protective layer.

A plaster thus contains:

Candesartan cilexetil	55.36 mg (equivalent to 40 mg of candesartan)
Copherol F1300	40 mg
Ethanol abs.	300.64 mg
Hydroxypropylcellulose	4 mg

Patent Claims

1. A transdermal therapeutic system with a content of candesartan or one of its pharmaceutically suitable esters or salts.

2. A transdermal therapeutic system according to claim 1, characterized by candesartan as active ingredient.

3. A transdermal therapeutic system according to claim 1, characterized by candesartan cilexetil as active ingredient.

4. A transdermal therapeutic system according to claim 1, characterized by the ammonium and/or alkali metal salts of candesartan as active ingredient.

5. A transdermal therapeutic system according to any of the preceding claims, characterized by candesartan or one of its pharmaceutically acceptable esters or salts as active ingredient in combination with other active ingredients.

6. A transdermal therapeutic system according to claim 5, characterized by at least one other active ingredient which enhances the effect of candesartan.

7. A transdermal therapeutic system according to claim 5 or 6, characterized by diuretics and/or Ca channel blockers as other active ingredients.

8. A transdermal therapeutic system according to any of the preceding claims in the form of a plaster with an impermeable covering layer and a detachable protective layer,

in particular in the form of a matrix system or of a membrane system.

9. A transdermal therapeutic system according to claim 8, characterized by a covering layer based on polyester, polypropylene, polyurethane or polyethylene, where appropriate in each case metalized or pigmented.

10. A transdermal therapeutic system according to claim 8, characterized by a detachable protective layer based on polyester, polypropylene, polysiloxane, polyacrylate, ethylene/vinyl acetate, polyurethane, polyisobutene or paper with silicone and/or polyethylene coating.

11. A transdermal therapeutic system according to claim 8, 9 or 10, characterized in that it is a matrix system with

- an impermeable covering layer,
- one or more active ingredient-containing contact adhesive matrix layer(s) or one or more active ingredient-containing matrix layer(s) coated with a contact adhesive,
- a detachable protective layer and
- candesartan or one of its pharmaceutically acceptable esters or salts as active ingredient.

12. A transdermal therapeutic system according to claim 11, characterized by a matrix layer based on polyacrylate, silicone, polyisobutylene, rubber, rubber-like synthetic homo-, co- or block polymers, butyl rubber, styrene/isoprene

copolymer, polyurethanes, copolymers of ethylene, polysiloxanes or styrene/butadiene copolymer.

13. A transdermal therapeutic system according to claim 8, 9 or 10, characterized in that it is a membrane system with

- an impermeable covering layer,
- an active ingredient-containing reservoir or an active ingredient-containing reservoir layer,
- a microporous or semipermeable membrane,
- an optional contact adhesive layer,
- candesartan or one of its pharmaceutically acceptable esters or salts as active ingredient.

14. A transdermal therapeutic system according to claim 13, characterized by a membrane based on an inert polymer, in particular polypropylene, polyvinyl acetate, polyamide, ethylene/vinyl acetate copolymer or silicone.

15. A transdermal therapeutic system according to any of the preceding claims, characterized by a permeation promoter, in particular monohydric and/or polyhydric aliphatic, cycloaliphatic and/or aromatic-aliphatic alcohols each with up to 8 C atoms, and/or polyethylene glycol; alcohol/water mixtures; saturated and/or unsaturated fatty alcohols each with 8-18 C atoms; terpenes; mixtures of terpenes and ethanol and/or propylene glycol; tea tree oil; saturated and/or unsaturated cyclic ketones; alkyl methyl sulfoxides; saturated and/or unsaturated fatty acids each with 8-18 C

atoms; the esters and salts thereof; natural vitamin E; synthetic vitamin E and/or vitamin E derivatives; sorbitan fatty acid esters and ethoxylated sorbitan fatty acid esters; Azone (laurocapram); Azone mixed with alcohols; urea; 1-alkylpyrrolidone; block copolymers of polyethylene glycol and dimethylsiloxane with cationic groups at one end; folate-polyethylene glycol liposome, proliposome; polyoxyethylene 10 stearyl ether; mixture of polyoxyethylene 10 stearyl ether and glyceryl dilaurate; dodecyl 2-(N,N-dimethylamino)propanoltetradecanoate and/or dodecyl 2-(N,N-dimethylamino)propionate; N-acetylprolinate esters with more than 8 C atoms; nonionic surfactants, esters of polyoxyethylene; ethosome (phospholipid vesicle); dimethyl(arylimino)sulfurane; mixture of oleic acid analogs and propylene glycol; mixture of padimate O, octyl salicylate, octyl methoxycinnamate and laurocapram and/or mixtures of all these components.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY Includes Reference to PCT International Applications	Attorney's Docket No. **4271-29PUS**

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

TRANSDERMAL THERAPEUTIC SYSTEM FOR THE ADMINISTRATION OF CANDESARTAN

the specification of which (check only one item below)

[] is attached hereto

[] was filed as United States application

Serial No. _

on _

and was amended

on _ (if applicable).

[x] was filed as PCT international application

Number PCT/EP99/03029

On 04 May 1999

And was amended under PCT Article 19

On _ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the patentability of the application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed.

PRIOR FOREIGN/PCT APPLICATIONS AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

Country (if PCT, indicate "PCT")	Application Number	Date of Filing (day, month, year)	Priority Claimed Under 35 U.S.C. 119	
Germany	198 20 151.6	06 May 1998	[x] YES	[] NO
PCT	PCT/EP99/03029	04 May 1999	[x] YES	[] NO
			[] YES	[] NO
			[] YES	[] NO
			[] YES	[] NO
			[] YES	[] NO
			[] YES	[] NO

Combined Declaration for Patent Application and Power of Attorney (Continued)
(Includes Reference to PCT International Applications)

Attorney's Docket No. **4271-29PUS**

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS *(check one)*		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. SERIAL NUMBERS ASSIGNED *(if any)*			
PCT/EP99/03029	04 May 1999				

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith (*List name and registration number*)

MYRON COHEN, Reg. No. 17,358; THOMAS C. PONTANI, Reg. No. 29,763; LANCE J. LIEBERMAN, Reg. No. 28,437; MARTIN B. PAVANE, Reg. No. 28,337; MICHAEL C. STUART, Reg. No. 35,698; KLAUS P. STOFFEL, Reg. No. 31,668; EDWARD M. WEISZ, Reg. No. 37,257; JULIA S. KIM, Reg. No. 36,567; VINCENT M. FAZZARI, Reg. No. 26,879; ALFRED W. FROEBRICH, Reg. No. 38,887; KENT H. CHENG, Reg. No. 33,849; GEORGE WANG, Reg. No. 41,419; TZVI HIRSHAUT, Reg. No. 38,732, GERALD J. CECHONY, Reg. No. 31,335; ROGER S. THOMPSON, Reg. No. 29,594; JOY I. FARBER, Reg. No. 44,103; and GEORGE J. BRANDT, JR., Reg. No. 22,021.

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202	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
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Combined Declaration for Patent Application and Power of Attorney (Continued) (Includes Reference to PCT International Applications)				Attorney's Docket No 4271-29PUS
203	FULL NAME OF INVENTOR	FAMILY NAME	FIRST GIVEN NAME	SECOND GIVEN NAME
	RESIDENCE, CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE & ZIP CODE/COUNTRY

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201	SIGNATURE OF INVENTOR 202	SIGNATURE OF INVENTOR 203
DATE 10/20/2000	DATE	DATE